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Signed R. Mahoney

Dated 1 April 2003

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21FEB02 E697590-1 C73568
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
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1. Your reference PAC 18

2. Patent application number
(The Patent Office will fill in this part) **0203994.9** 20 FEB 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CELLTECH R&D LIMITED
208 BATH ROAD
SLOUGH
BERKSHIRE, SL1 3WE
U.K.

8121485001

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Mrs: HANNAH KENDALL
CELLTECH R&D LIMITED
GRANTA PARK
GREAT ABINGTON
CAMBRIDGE, CB1 6GS

8144198001

Patents ADP number *(if you know it)* —

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
—	—	—

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
—	—

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	38
Claim(s)	3
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

FOR AND ON BEHALF OF CELLTECH R&D LIMITED

Signature Mangery Hanley Date 20/02/02

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS HANNAH KENDALL
01223 896499

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Chemical Compounds

This invention relates to a series of cyclic amino derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that chemokines (chemotactic cytokines) play a key role in the recruitment and activation of a variety of cell types in inflammatory processes, for example recruitment of eosinophils in the tissue eosinophilia that is a feature of a number of pathological conditions including asthma, rhinitis, eczema and parasitic infections. Further certain chemokines have been implicated in a variety of autoimmune diseases, such as rheumatoid arthritis, irritable bowel disease and multiple sclerosis as well as playing a critical role in the pathway of viral infection, such as invasion by HIV. [Schwarz, M. K. and Wells, T. N. C., Curr. Opin. Chem. Biol., 1999, 3, 407-17; Bousquet, J. *et al*, N. Eng. J. Med., 1990, 323, 1033-39; Kay, A. B. and Corrigan, C. J., Br. Med. Bull., 1992, 48, 51-64].

Chemokines are released by a wide variety of cells to attract and activate, among other cell types, macrophages, T and B lymphocytes, eosinophils, basophils and neutrophils [Luster, New Eng. J. Med., 1998, 338, 436-45; Rollins, Blood, 1997, 90, 909-28]. To date almost 40 human chemokines have been well characterised [Schwarz, M. K., *ibid*; Wells, T. N. C. *et al*, Trends Pharmacol Sci, 1998, 19, 376-380] and they have been classified into two major classes, CXC and CC, depending on whether the first two cysteines in the amino acid sequence are separated by a single amino acid (CXC) or are adjacent (CC). Members of two additional classes, C chemokines (lymphotactin-1 and lymphotactin-2) and a CX3C chemokine (fractalkine) have also been identified. It was initially thought that CXC chemokines, such as IL-8 (a neutrophil attractant), were associated with acute inflammation whilst CC chemokines were associated with chronic inflammatory diseases such as asthma, arthritis and atherosclerosis. However it is now known that members of both classes are involved in both chronic and acute inflammation.

In general the CXC chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activating protein (MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas CC chemokines such as RANTES (regulation-upon-activation, normal T-cell expressed and secreted), MIP-1α, MIP-1β, the monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3, MCP-4, MCP-5) and the eotaxins (-1, -2 and –3) are chemotactic for macrophages, T lymphocytes, eosinophils, dendritic cells and basophils.

The chemokines bind to specific cell-surface receptors. Seventeen mammalian receptors have been reported to date [Schwarz, M. K. *ibid*], all of which are seven-transmembrane-spanning G-protein coupled receptors. The ligand binding characteristics of these receptors has been identified, for example the ligands for CCR-1 are RANTES, MIP-1α and MCP-3 whilst those for CCR-2 are MCP-1, 2, 3, 4 and 5.

Chemokines and their receptors have been implicated as important mediators of inflammatory, infectious, and immunoregulatory diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

The CXCR3 chemokine receptor is expressed primarily in T lymphocytes, and its functional activity can be measured by cytocolic calcium elevation or chemotaxis. The receptor was previously referred to as GPR9 or CKR-L2. Its chromosomal location is unusual among the chemokine receptors in being localised to Xq13. Ligands that have been identified that are selective and are of high affinity are the CXC chemokines, interferon-gamma inducible protein (IP10), monokine induced by interferon-gamma (MIG) and interferon-inducible T cell alpha chemoattractant (ITAC).

The highly selective expression of CXCR3 makes it an ideal target for the intervention to interrupt inappropriate T cell trafficking. The clinical indications for such intervention are in T-cell mediated diseases such as multiple sclerosis, rheumatoid arthritis and type I diabetes. Inappropriate T-cell

infiltration also occurs in psoriasis and other pathogenic skin inflammation conditions, although the diseases may not be true autoimmune disorders. In this regard, up-regulation of IP-10 expression in keratinocytes is a common feature in cutaneous immunopathologies. Inhibition of CXCR3 can be beneficial in reducing rejection in organ transplantation. Ectopic expression of CXCR3 in certain tumours, especially subsets of B-cell malignancies indicate that selective inhibitors of CXCR3 will have value in tumour immunotherapy, particularly attenuation of metestasis. [See, for example, Qin S. et al, J. Clin. Invest, 1998, 101, 746-754; Sørenson T.L. et al, J. Clin. Invest, 1999, 103, 807-815.]

Accordingly in view of the clinical importance of CXCR3 there is a great need for new therapeutic agents that modulate CXCR3 function. We have found a class of cyclic amino derivatives that are potent modulators of the interaction between CXCR3 and its chemokine ligands. The compounds are thus of use in medicine, for example in the prevention or treatment of certain inflammatory, autoimmune and immunoregulatory disorders as desciribed hereinafter.

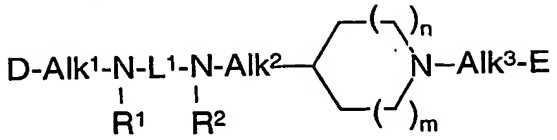
European Patent specifcation no. 516520 discloses a class of urea derivatives for use as acetylcholinesterase inhibitors.

European Patent specifcation no. 625507 discloses a general class of urea derivatives for use as ACAT inhibitors.

US patent specifcation no. 3,424,761 discloses a class of 3-ureidopyrrolidines characterised by analgetic, central nervous system and psychpharmacologic activities.

US patent specifcation no. 6,329,395 discloses a general class of ureas for use as neuropeptide Y5 receptor antagonists.

Thus according to the first aspect of the invention we provide a compound of formula (1):



(1)

wherein:

m and n, which may be the same or different, is each zero or the integer 1 or 2;

Alk^1 is a covalent bond or an optionally substituted aliphatic chain;

Alk^2 and Alk^3, which may be the same or different, is each a covalent bond or a straight or branched C_{1-6} alkyl chain;

R^1 and R^2, which may be the same or different, is each a hydrogen atom or a straight or branched C_{1-6} alkyl group;

L^1 is a linker group selected from –CO-, -CS-, $-SO_2-$ or $-C(=NR^3)-$, wherein R^3 is a –CN, $-COR^4$, $-OR^5$, $-CON(R^6)R^7$, SO_2R^4 or $SO_2N(R^6)R^7$ group, in which R^4 is an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, R^5 is a hydrogen atom or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group and R^6 and R^7, which may be the same or different, is each a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

D is an optionally substituted aromatic or heteroaromatic group;

E is a substituted C_6 cycloalkyl or an optionally substituted C_{7-10} cycloalkyl, C_{6-10} cycloalkenyl, C_{6-10} polycycloaliphatic, C_{6-10} heterocycloaliphatic or C_{6-10} heteropolycycloaliphatic group;

and the salts, solvates, hydrates, tautomers or N-oxides thereof;

for use in the treatment of a CXCR3 mediated disorder.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers) The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all

individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example urea (-NHC(O)NH-) – (-NC(OH)NH-) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected carboxylic acid derivative, e.g. as an acceptable ester. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs. Such prodrugs are well known in the literature, see for example International Patent Application No. WO 00/23419, Bodor N. (Alfred Benson Symposium, 1982, 17, 156-177), Singh G. *et al* (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard H. (Design of Prodrugs, 1985, Elsevier, Amsterdam).

In the compounds for use in the invention and as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

Thus as used herein the term "alkyl", whether present as a group or part of a group includes straight or branched C_{1-10}alkyl groups, for example C_{1-6}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl or neopentyl groups. Optional substituents when present on those groups include those optional substituents mentioned hereinafter.

The term "aliphatic group" is intended to include optionally substituted straight or branched C_{1-10}alkyl, e.g. C_{1-6} alkyl, C_{2-10}alkenyl e.g. C_{2-6}alkenyl or C_{2-10} alkynyl e.g. C_{2-6}alkynyl groups.

Particular examples of aliphatic groups include optionally substituted C_{1-6} alkyl groups such as $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-C(CH_3)_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$ or C_{2-6}alkenyl or C_{2-6}alkynyl groups such as $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$, $-C(CH_2)CH_3$, $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, or $-(CH_2)_2CCH$.

The term "aliphatic chain" is intended to include those alkyl, alkenyl or alkynyl groups as previously described where a terminal hydrogen atom is replaced by a covalent bond to give a divalent chain.

Examples of aliphatic chains include optionally substituted C_{1-6} alkyl chains such as $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$ or C_{2-6}alkenyl or C_{2-6}alkynyl chains such as $-CHCH-$, $-CHCHCH_2$ $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ chains. More particular examples include optionally substituted C_{1-3} alkyl chains selected from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-C(CH_3)_2-$ and $-CH_2CH(CH_3)-$ chains.

The term "heteroaliphatic group" is intended to include the optionally substituted aliphatic groups just described but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples of suitable L^2 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O), $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or a C_{1-6} alkyl group], $-N(R^8)N(R^8)-$,

$-N(R^8)O-$, $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$ groups. Where the linker group contains two R^8 substituents, these may be the same or different.

Particular examples of heteroaliphatic groups include optionally substituted $-L^2CH_3$, $-CH_2\ L^2CH_3$, $-\ L^2CH_2CH_3$, $-\ L^2CH_2CHCH_2$, $-\ L^2CH_2CCH$, $-CH_2\ L^2CH_2CH_3$, $-\ L^2CH_2L^2CH_3$, $-(CH_2)_2L^2CH_3$, $-\ L^2(CH_2)_2CH_3$ and $-(CH_2)_2\ L^2CH_2CH_3$ groups.

The term "cycloaliphatic group" includes optionally substituted non-aromatic cyclic or multicyclic, saturated or partially saturated C_{3-10} ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, adamantyl, norbornyl, norbornenyl, bicyclo[2.2.1]heptanyl or bicyclo[2.2.1]heptenyl. Particular examples include optionally substituted C_{3-6} cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on those groups include those substituents mentioned hereinafter.

The term "heterocycloaliphatic group" refers to an optionally substituted 3 to 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, three or four L^3 linker atoms or groups. Particular examples of suitable L^3 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{14})-$ [where R^{14} is a hydrogen atom or a C_{1-6} alkyl group], $-N(R^{14})N(R^{14})$, $-N(R^{14})O-$, $-ON(R^{14})-$, $-CON(R^{14})-$, $-OC(O)N(R^{14})-$, $-CSN(R^{14})-$, $-N(R^{14})CO-$, $-N(R^{14})C(O)O-$, $-N(R^{14})CS-$, $-S(O)_2N(R^{14})-$, $-N(R^{14})S(O)_2-$, $-N(R^{14})CON(R^{14})-$, $-N(R^{14})CSN(R^{14})-$, $-N(R^{14})SO_2N(R^{14})-$ groups. Where the linker group contains two R^{14} substituents, these may be the same or different. Optional substituents present on the heterocyloaliphatic groups include those substituents mentioned hereinafter.

Particular examples of heterocycloaliphatic groups include optionally substituted cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, pyranonyl, piperidinyl, piperidinonyl, quinuclidinyl, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C_{1-6} alkylpiperazinyl, homopiperazinyl, dihydrofuran-2-onyl, tetrahydropyran-2-onyl, isothiazolidinyl 1,1-dioxide, [1,2]thiazinanyl 1,1-dioxide, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrazolidin-3-onyl, tetrahydrothiopyranyl 1,1-dioxide, tetrahydrothiophenyl 1,1-dioxide, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the alkyl, aliphatic, heteroaliphatic, cycloaliphatic or heterocycloaliphatic groups, include one, two, three or more substituents, which each may be the same or different, selected from halogen atoms, or alkoxy, haloalkyl, haloalkoxy, hydroxy (-OH), thiol (-SH), alkylthio, amino(-NH_2), substituted amino, optionally substituted C_{6-12}arylamino, optionally substituted C_{1-6} alkyl, -CN, -CO_2H, -CO_2R^9 (where R^9 is an optionally substituted C_{1-6} alkyl group), -SO_3H, -SOR^{10} (where R^{10} is a C_{1-6} alkyl group) -SO_2R^{10}, -SO_3R^{10}, -OCO_2R^{10}, -C(O)H, -$C(O)R^{10}$, -$OC(O)R^{10}$, -$C(S)R^{10}$, -$C(O)N(R^{11})(R^{12})$ (where R^{11} and R^{12}, which may be the same or different is each a hydrogen atom or a C_{1-6} alkyl group), -$OC(O)N(R^{11})(R^{12})$, -$N(R^{11})C(O)R^{12}$, -$CSN(R^{11})(R^{12})$, -$N(R^{11})C(S)(R^{12})$, -$SO_2N(R^{11})(R^{12})$, -$N(R^{11})SO_2R^{12}$, -$N(R^{11})C(O)N(R^{12})(R^{13})$ (where R^{13} is a hydrogen atom or a C_{1-6} alkyl group), -$N(R^{11})C(S)N(R^{12})(R^{13})$, -$N(R^{11})SO_2N(R^{12})(R^{13})$, or an optionally substituted aromatic or heteroaromatic group. Substituted amino groups include –NHR^{10} and -$N(R^{10})(R^{11})$ groups.

Cycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon atom. Heterocycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon or, where available, ring nitrogen atom.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CH_2F$, and $-CH_2Cl$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-10}alkoxy for example C_{1-6}alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-10}alkylthio, e.g. C_{1-6}alkylthio such as methylthio or ethylthio groups.

The terms "aromatic group" and "aryl group" are intended to include for example optionally substituted monocyclic ring C_{6-12} aromatic groups, such as phenyl, or bicyclic fused ring C_{6-12} aromatic groups, such as, 1- or 2-naphthyl groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms (or oxidised versions thereof). In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for

example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Each of these aromatic or heteroaromatic groups may be optionally substituted by one, two, three or more R^{16} atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, or triazinyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothienyl, benzotriazolyl, indolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl or phthalazinyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups include one, two, three or more substituents, each selected from an atom or group R^{16} in which R^{16} is -R^{16a} or –$Alk^4(R^{16a})_f$, where R^{16a} is a halogen atom, or an amino (-NH_2), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, amidino, formyl, carboxyl (-CO_2H), esterified carboxyl, thiol (-SH), substituted thiol, -COR^{17} [where R^{17} is an –$Alk^4(R^{16a})_f$, heterocycloaliphatic, cycloaliphatic, aryl or heteroaryl group], -CSR^{17}, -SO_3H, -SOR^{17}, -SO_2R^{17}, -SO_3R^{17}, -SO_2NH_2, -SO_2NHR^{17}, $SO_2N(R^{17})_2$, -$CONH_2$, -$CSNH_2$, -$CONHR^{17}$, -$CSNHR^{17}$, -$CON(R^{17})_2$, -$CSN(R^{17})_2$, -$N(R^{18})SO_2R^{17}$, [where R^{17} is a hydrogen atom or a C_{1-6} alkyl group] -$N(SO_2R^{17})_2$, -$N(R^{18})SO_2NH_2$, -$N(R^{18})SO_2NHR^{17}$, -$N(R^{17})SO_2N(R^{18})_2$, -$N(R^{18})COR^{17}$, -$N(R^{18})CONH_2$, -$N(R^{18})CONHR^{17}$, -$N(R^{18})CON(R^{17})_2$, -$N(R^{18})CSNH_2$,

$-N(R^{18})CSNHR^{17}$, $-N(R^{18})CSN(R^{17})_2$, $-N(R^{18})CSR^{17}$, $-N(R^{18})C(O)OR^{17}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{3-7}heterocycloaliphatic group containing at least one N atom and optionally containing one or more other -O- or -S- atoms or $-N(R^{18})-$, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{14})SO_2NHet^1$, $-N(R^{18})CONHet^1$, $-N(R^{18})CSNHet^1$, $-SO_2N(R^{18})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{3-7} cycloalipatic group optionally containing one or more -O- or -S- atoms or $-N(R^{18})-$, -C(O)- or -C(S)- groups], $-Het^2$, $-CON(R^{18})Het^2$, $-CSN(R^{18})Het^2$, $-N(R^{18})CON(R^{18})Het^2$, $-N(R^{18})CSN(R^{18})Het^2$, aryl or heteroaryl group; Alk^4 is a straight or branched C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_g-$ [where g is an integer 1 or 2] or $-N(R^{18})-$ groups; and f is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{17} or R^{18} groups are present in one of the above substituents, the R^{17} or R^{18} groups may be the same or different.

When in the group $-Alk^4(R^{16a})_f$ f is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{16a} may be present on any suitable carbon atom in $-Alk^4$. Where more than one R^{16a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^4$. Clearly, when f is zero and no substituent R^{16a} is present the alkyl, alkenyl or alkynyl chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

When R^{16a} is a substituted amino group it may be for example a group $-NHR^{17}$ [where R^{17} is as defined above] or a group $-N(R^{17})_2$ wherein each R^{17} group is the same or different.

When R^{16a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{17}$ or a $-SR^{17}$ group respectively.

Esterified carboxyl groups represented by the group R^{16a} include groups of formula $-CO_2Alk^5$ wherein Alk^5 is an optionally substituted alkyl group.

When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^{15})-$ groups.

When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{16} each may be for example an optionally substituted 2- or 3-pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperazinyl, imidazolinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ or $-Het^2$ include those substituents described above in relation to aromatic groups.

Particularly useful atoms or groups represented by R^{16} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl or piperidinyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkylamino e.g. aminoethylamino, Het^1NC_{1-6}alkylamino e.g. morpholinopropylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6} dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy,

diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino e.g. hydroxyethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^5 [where Alk^5 is as defined above], C_{1-6}alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH_2, sulphonyl (-SO_3H), -SO_3R^{18}, C_{1-6}alkylsulphinyl e.g. methylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylamino-sulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethyl-aminosulphonyl or diethylaminosulphonyl, optionally substituted phenylamino-sulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylamino-carbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethyl-aminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylamino-carbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethyl-aminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylamino-carbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonyl-amino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH_2, C_{1-6}alkyl-sulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonyl-amino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkyl-

aminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, benzylamino, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two adjacent R^{16} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy or a C_{3-6} cycloalkyl or 3-10 membered monocylic heterocycloaliphatic group as defined herein.

It will be appreciated that where two or more R^{16} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium

or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

The cycloalkyl and cycloalkenyl groups represented by E include non-aromatic cyclic or multicyclic, saturated or partially saturated C_{6-10} cycloalkyl or C_{6-10} cycloalkenyl ring systems as generally and particularly described above. The term "C_{6-10} heterocycloaliphatic group" is intended to include the C_{6-10} cycloalkyl or C_{6-10} cycloalkenyl groups just described, but with each group additionally containing one, two, three or four L^4 atoms or groups. Particular examples of suitable L^4 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-CON(R^{15})-$ [where R^{15} is a hydrogen atom or a C_{1-6} alkyl group], $-OC(O)N(R^{15})-$, $-CSN(R^{15})-$, $-N(R^{15})CO-$, $-N(R^{15})C(O)O-$, $-N(R^{15})CS-$, $-S(O)_2N(R^{15})-$, $-N(R^{15})S(O)_2-$, $-N(R^{15})CON(R^{15})-$, $-N(R^{15})CSN(R^{15})-$, $-N(R^{15})SO_2N(R^{15})-$ groups. Where the linker group contains two R^{15} substituents, these may be the same or different. Where appropriate the cycloalkyl, cycloalkenyl and heterocycloaliphatic groups may be substituted with one or more substituents as described hereinafter.

The C_{6-10} polycycloaliphatic groups represented by E include optionally substitued C_{6-10}bi- or tricycloalkyl or C_{6-10}bi- or tricycloalkenyl groups. The term "C_{6-10} heteropolycycloaliphatic group" is intended to include the optionally substituted C_{6-10} polycycloaliphatic groups just described, but with each group additionally containing one, two, three or four L^4 atoms or groups.

Examples of groups represented by E include, but are not limited to, substituted cyclohexyl or optionally substituted cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, adamantyl, adamantanonyl, noradamantyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptanyl, bicyclo[3.1.1]heptenyl, bicyclo[2.2.2]octanyl,

bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octanyl, bicyclo[3.2.1]octenyl, bicyclo[3.3.1]nonanyl, bicyclo[6.2.0]decanyl, octahydro-4,7-methanoindenyl, octahydronaphthalenyl, dihydropyranyl, tetrahydropyranyl, cyclohexanonyl, cycloheptanonyl, cyclooctanonyl, tetrahydropyran-2-onyl, bicyclo[2.2.1]heptanonyl, bicyclo[3.1.1]heptanonyl, bicyclo[2.2.2]octanonyl, bicyclo[3.2.1]octanonyl, bicyclo[3.3.1]nonanonyl, 1,4-dioxaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decenyl.

Optional substituents which may be present on the group E include one, two, three or more substituents, which each may be the same or different, selected from alkoxy, haloalkyl e.g. $-CF_3$, $-CF_2H$, haloalkoxy e.g. $-OCF_2H$, hydroxy (-OH), thiol (-SH), alkylthio, optionally substituted straight or branched C_{1-6} alkyl or C_{2-6} alkenyl, -CN, $-CO_2H$, $-CO_2R^{9a}$ (where R^{9a} is an optionally substituted C_{1-6} alkyl group), $-SO_3H$, $-SOR^{10a}$ (where R^{10a} is a C_{1-6} alkyl group) $-SO_2R^{10}$, $-SO_3R^{10}$, $-OCO_2R^{10}$, -C(O)H, $-C(O)R^{10}$, $-OC(O)R^{10}$, $-C(S)R^{10}$, $-C(O)N(R^{11a})(R^{12a})$ (where R^{11a} and R^{12a}, which may be the same or different is each a hydrogen atom or a C_{1-6} alkyl group), $-N(R^{11a})C(O)R^{12a}$, $-CSN(R^{11a})(R^{12a})$, $-N(R^{11a})C(S)(R^{12a})$, $-SO_2N(R^{11a})(R^{12a})$, $-N(R^{11a})SO_2R^{12a}$, $-N(R^{11a})C(O)N(R^{12a})(R^{13a})$ (where R^{13a} is a hydrogen atom or a C_{1-6} alkyl group), $-N(R^{11a})C(S)N(R^{12a})(R^{13a})$, $-N(R^{11a})SO_2N(R^{12a})(R^{13a})$, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

Examples of optionally substituted alkyl groups present in ester groups of formulae $-CO_2R^9$, $-CO_2R^{9a}$ and $-CO_2Alk^5$ include C_{1-6} alkyl groups as herein described. Optional substituents which may be present on these alkyl groups include optionally substituted cycloaliphatic, aromatic or heteroaromatic groups as herein defined.

Examples of optionally substituted aliphatic chains represented by Alk^1 include straight or branched C_{1-6} alkyl chains as herein described. More

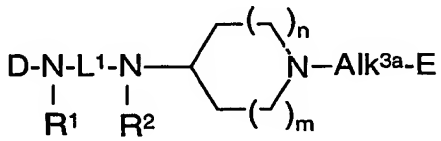
particular examples include C_{1-3} alkyl chains, such as $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH(CH_3)CH_2-$, especially $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. Particular substituents, when present, include C_{1-3} alkoxy, hydroxy, optionally substituted phenyl or monocyclic heteroaromatic or optionally substituted straight or branched C_{1-3} alkyl, where the optional alkyl substituent is in particular an optionally substituted phenyl or monocyclic heteroaromatic group.

Alk^2, when present in compounds of formula (1), is preferably a C_{1-3} alkyl chain, particularly $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$.

In one group of compounds for use in the invention Alk^2 is a covalent bond.

Alk^3 in one group of compounds of formula (1) is preferably a C_{1-3} alkyl chain, in particular $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, more particularly $-CH_2-$. Alternatively Alk^3 in another group of compounds of formula (1) is a covalent bond.

One particular group of compounds for use in the invention has the formula (2):



(2)

wherein m,n, R^1, R^2, L^1, D and E are as herein defined;
Alk^{3a} is a C_{1-3} alkyl chain;
and the salts, solvates, hydrates, tautomers or N-oxides thereof.

In compounds of formulae (1) or (2) m and n, which may be the same or different, is each in particular zero or the integer 1. In particular m and n is each the integer 1.

R^1 and R^2, which may be the same or different, is each preferably a hydrogen atom or a straight or branched C_{1-3} alkyl group, especially methyl.

L^1 in compounds of formulae (1) or (2) is in particular a linker group selected from –CO-, -CS-, $-SO_2-$ or $-C(=NR^3)-$, wherein R^3 is a –CN, $-COR^4$, $-OR^5$, $-CON(R^6)R^7$, SO_2R^4 or $SO_2N(R^6)R^7$ group, in which R^4 is an optionally substituted C_{1-3} alkyl, C_{3-6} cycloalkyl, 3 to 7 membered heterocycloalkyl, aromatic or heteroaromatic group, R^5 is a hydrogen atom or an optionally substituted C_{1-3} alkyl, C_{3-6} cycloalkyl, 3 to 7 membered heterocycloalkyl, aromatic or heteroaromatic group and R^6 and R^7, which may be the same or different, is each a hydrogen atom or an optionally substituted C_{1-3} alkyl, C_{3-6} cycloalkyl, 3 to 7 membered heterocycloalkyl, aromatic or heteroaromatic group. R^3 for use in compounds of the invention is especially a –CN or $-OR^5$ group, particularly a –CN group.

L^1 in compounds of formulae (1) or(2) is especially a –CO- or –CS- group, particularly a –CO- group.

One group of compounds for use in the invention has the formulae (1) or (2) wherein D is selected from optionally substituted phenyl, 1- or 2-naphthyl, pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, benzofuryl, benzothienyl, benzotriazolyl, indolyl, indazolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl or isoquinolinyl. More particular D groups include optionally substituted phenyl, 1- or 2-naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, quinolinyl or isoquinolinyl.

In one goup of compounds of formulae (1) or (2) D is especially an optionally substituted phenyl or 2-naphthyl group.

Particular aromatic or heteroaromatic substituents, which may be present on the group D, are one, two, three or more atoms or groups selected from fluorine, chlorine, bromine, optionally substituted straight or branched C_{1-3} alkyl (wherein the optional alkyl substituent is in particular an optionally substituted phenyl or monocyclic heteroaryl group), optionally substituted phenyl, monocyclic heteroaryl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, methoxy, phenoxy, pyridyloxy, benzoyl, pyridoyl or $COCH_3$, OCF_3, OCF_2H, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, CO_2H or two adjacent substituents are linked together to form methylenedioxy, ethylenedioxy or cyclopentyl. More particular D substituents are selected from fluorine, chlorine, CF_3, methyl, methoxy, OCF_2H, OCF_3 or optionally substituted phenyl, monocyclic heteroaryl, phenoxy or pyridyloxy. The monocyclic heteroaryl substituents in compounds of this type are in particular selected from pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl or thienyl.

Particular examples of D groups include 3,4-dichlorobenzene, 3- or 4-chlorobenzene or 3- or 4-trifluoromethylbenzene.

Particular substituents, which may be present on the group E, are one, two, three or more groups selected from hydroxy, or optionally substituted phenyl or monocyclic heteroaromatic, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, CO_2H or optionally substituted straight or branched C_{1-6} alkyl or C_{2-6} alkenyl, wherein the optional alkyl or alkenyl substituent is in particular an optionally substituted phenyl or monocyclic heteroaromatic group. Particular examples of the optionally substituted C_{1-6} alkyl or C_{2-6} alkenyl groups are $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-C(CH_3)_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$ $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$ or $-C(CH_2)CH_3$.

One group of compounds has the formulae (1) or (2) wherein E is selected from optionally substituted cycloheptyl, cyclooctyl, cyclononyl, cyclohexenyl,

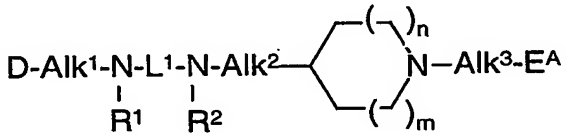
cycloheptenyl, cyclooctenyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptanyl or bicyclo[3.1.1]heptenyl.

One preferred group of compounds is where E is substituted with one, two, three or more methyl groups.

E in one particular group of compounds for use in the invention is a 1-cyclooctenyl or 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl group.

One particular set of aromatic or heteroaromatic substituents, which may be present on compounds of formulae (1) or (2), are one, two, three or more atoms or groups selected from fluorine, chlorine, bromine, straight or branched C_{1-3} alkyl, methoxy, OCF_3, OCF_2H, CF_3, CN, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$ or CO_2H.

According to another aspect of the invention we provide a compound of formula (3) :



(3)

wherein:

m and n, which may be the same or different, is each zero or the integer 1 or 2;

Alk^1 is a covalent bond or an optionally substituted aliphatic chain;

Alk^2 and Alk^3, which may be the same or different, is each a covalent bond or a straight or branched C_{1-6} alkyl chain;

R^1 and R^2, which may be the same or different, is each a hydrogen atom or a straight or branched C_{1-6} alkyl group;

L^1 is a linker group selected from –CO-, -CS-, $-SO_2-$ or $-C(=NR^3)-$, wherein R^3 is a –CN, $-COR^4$, $-OR^5$, $-CON(R^6)R^7$, SO_2R^4 or $SO_2N(R^6)R^7$ group, in which R^4 is an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, R^5 is a hydrogen atom or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic,

heterocycloaliphatic, aromatic or heteroaromatic group and R^6 and R^7, which may be the same or different, is each a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

D is an optionally substituted aromatic or heteroaromatic group;

E^A is an optionally substituted C_{7-10} cycloalkyl, C_{6-10} cycloalkenyl, C_{6-10} polycycloaliphatic, C_{6-10} heterocycloaliphatic or C_{6-10} heteropolycycloaliphatic group; or E^A is additionally a substituted C_6 cycloalkyl group when the sum of m+n is zero or 2, 3 or 4;

and the salts, solvates, hydrates, tautomers or N-oxides thereof;

It will be appreciated that all discussion and preferences herein relating to the compounds of formulae (1) and (2) and their various individual substituents also apply to the compounds of formula (3) where still structurally applicable. In compounds of formula (3) E^A is as generally and specifically defined for E.

One particular group of compounds of the invention includes:
1-[1-((E)-1-Cyclooct-1-enyl)methylpiperidin-4-yl]-3-(3,4-dichlorophenyl)-urea;
1-[1-((E)-1-Cyclooct-1-enyl)methyl-piperidin-4-yl]-3-(4-trifluoromethylphenyl)-urea;
and the salts, solvates, hydrates, tautomers or N-oxides thereof;

Compounds according to the invention are potent and selective inhibitors of chemokine binding the CXCR3 receptor. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating chemokine mediated cell signalling and in particular are of use in the prophylaxis and/or treatment of diseases or disorders involving inappropriate T-cell trafficking. The invention extends to such a use and to the use of the compounds of formulae (1), (2) or (3) for the manufacture of a medicament for treating such diseases and disorders. Particular diseases include inflammatory, autoimmune and immunoregulatory disorders.

Particular uses to which the compounds of the invention may be put include: (1) inflammatory or allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies; inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis; vaginitis; psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis; spondyloarthropathies; scleroderma; respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases and the like. (2) autoimmune diseases, such as arthritis (rheumatoid and psoriatic), multiple sclerosis, systemic lupus erythematosus, diabetes, glomerulonephritis and the like. (3) graft rejection (including allograft rejection and graft-v-host disease), and (4) other diseases in which undesired inflammatory responses are to be inhibited (e.g. atherosclerosis, myositis, neurodegenerative diseases, Alzheimer's disease, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis and Behcet's syndrome).

In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of multiple sclerosis, psoriasis, rheumatoid arthritis, allograft rejection and graft-v-host disease.

The compounds of formulae (1), (2) or (3) can be used alone or in combination with other compounds having related utilities to prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as multiple sclerosis, rheumatoid arthritis and atherosclerosis, and those pathologies as discussed herein.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical

composition which comprises a compound of formulae (1), (2) or (3) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Alternate compositions of this invention comprise a compound of formulae (1), (2) or (3) or a salt thereof; an additional agent selected from an immunosuppressant or an anti-inflammatory agent; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formulae (1), (2) or (3) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of formulae (1), (2) or (3) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formulae (1), (2) or (3) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formulae (1), (2) or (3) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

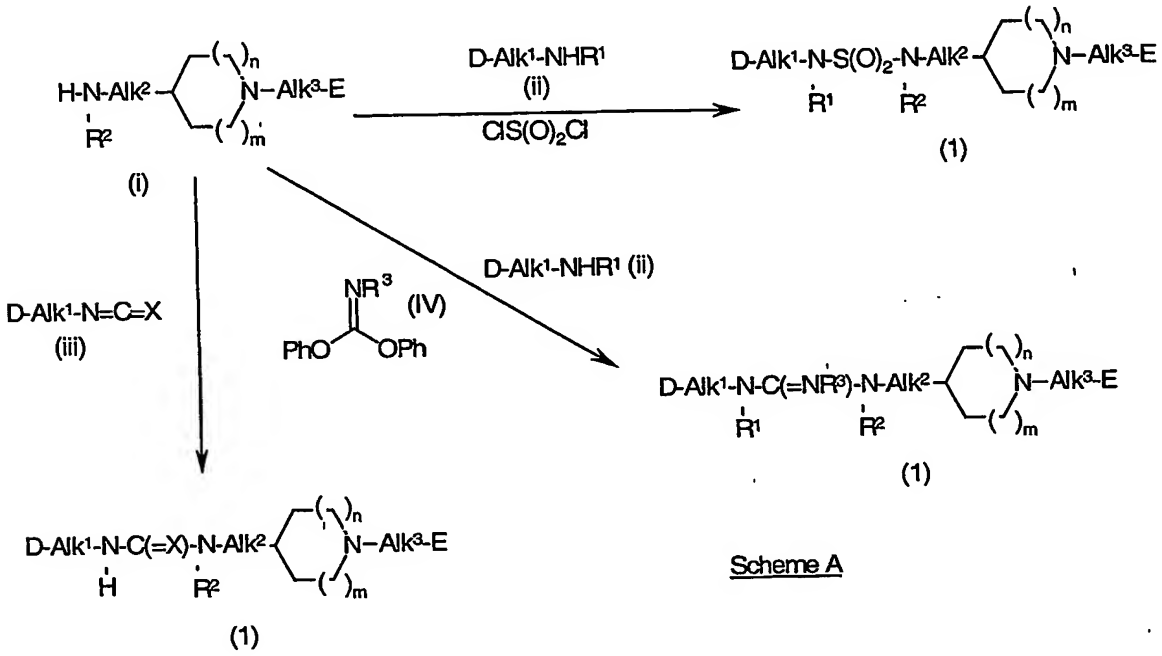
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

In the following process description, the symbols D, E, Alk^1, Alk^2, Alk^3, L^1, n, m, R^1-R^3 when used in the formulae depicted are to be understood to represent those groups described above in relation to formulae (1), (2) or (3) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formulae (1), (2) or (3) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1), (2) or (3) may be prepared from an amine of general formula (i) using the general method as shown in Scheme A:



Scheme A

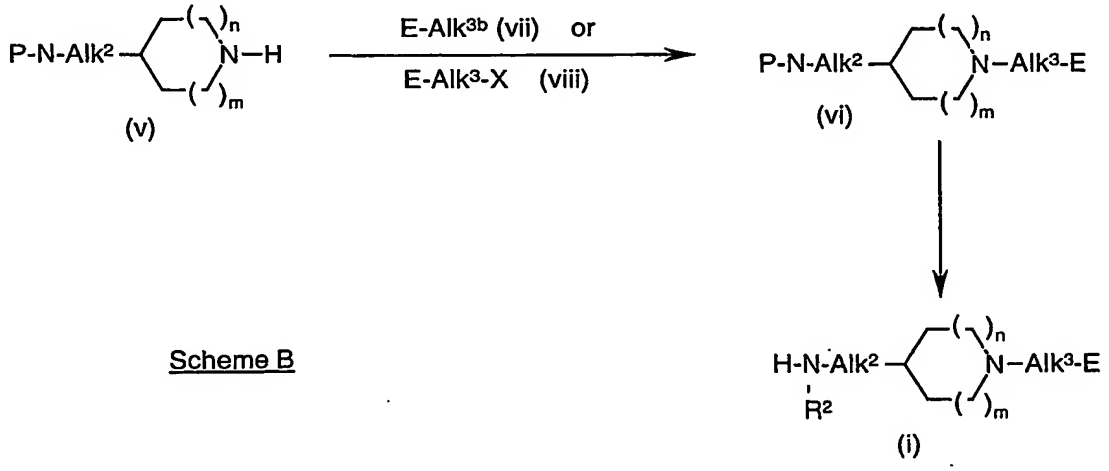
Thus, for example, an amine of formula (i) may be reacted with sulfuryl chloride followed by addition of an amine of general formula (ii) to give a compound of formula (1) where L^1 is a $-SO_2-$ group. Appropriate conditions involve the use of an amine base e.g. triethylamine in a solvent such as a halogenated hydrocarbon e.g. dichloromethane.

Alternatively an amine of formula (i) may be reacted with an isocyanate or isothiocyanate of general formula (iii) (where X is a O or S atom) in the presence of an amine base e.g. triethylamine in a solvent such as a halogenated hydrocarbon e.g. dichloromethane to give a compound of general formula (1) where L^1 is –CS- or –CO-.

Further, an amine of formula (i) may be reacted with a substituted diphenyl carbonimidate (iv) e.g. commercially available diphenyl *N*-cyanocarbonimidate under appropriate conditions such as room temperature in acetonitrile, to afford an intermediary isourea. This isourea may then be converted to the

desired guanidine of general formula (1), for example, by either heating with an amine of formula (ii) at 80°C for 2 hours or by treatment with an amine of formula (ii) in refluxing dioxane for 18 hours. Alternatively the order of reactions may be reversed so that amine (i) may be first reacted with a substituted diphenyl carbonimidate (iv) and the resulting intermediary isourea then treated with an amine of general formula (i). See, for example, Parmee *et al* Bioorganic & Medicinal Chemistry Letters 11, 2001, 379-382. It will be appreciated that the alternative guanidines of formula (1) may be prepared using suitable methods known to those skilled in the art, for example, see Garrett *et al* Tetrahedron, 1993, 49, 6885-6898; Townsend *et al*, J. Org. Chem. 1988, 53, 5622-5628; Farmaco Ed. Sci. 1988, 43, 575-596 for general methodologies.

The amine of general formula (i) may be prepared using the general Scheme B as shown below:



Scheme B

Thus, an amine of general formula (v) where P is a suitable protecting group e.g. tert-butoxycarbonyl, may be reacted with a compound of formula E-Alk^3-X (viii), wherein X is a suitable leaving group (e.g. a halogen, such as chlorine or bromine, or an arylsulfonyloxy group, such as *p*-toluene sulfonate) to give a compound of general formula (vi). The reaction may be performed in the presence of a base, such as potassium carbonate in, for example, refluxing acetonitrile.

Alternatively a compound of general formula (vi) may be prepared by reductive alkylation of a compound of formula (v) with a compound of formula E-Alk^{3b} (vii), wherein Alk^{3b} is a suitable precursor to Alk^3, for example Alk^{3b} contains a reactive group, such as a reactive carbonyl. This reaction may be achieved using methods known to those skilled in the art. For example, when Alk^{3b} incorporates an aldehyde, appropriate conditions may include the use of a suitable borohydride as reductant, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. methanol or ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

The compounds of formula (viii) may be prepared from an alcohol of general formula E-Alk^3-OH (ix) using standard methodology known to those skilled in the art. For example, when X is an arylsulfonate ester, this may be prepared by reaction of the alcohol (ix) with *p*-toluenesulfonyl chloride in the presence of an amine base, e.g. triethylamine in an appropriate solvent, such as dichloromethane or tetrahydrofuran.

The compounds of formula (ix) may also be used to prepare the compounds of formula (vii) using standard oxidising conditions such as those described herein.

The compound of formula (vi) may be deprotected using standard methodology to give an amine of general formula (i) wherein R^2 is a hydrogen atom. This may be alkylated using standard techniques known to those skilled in the art to give an amine of formula (vi) wherein R^2 is an alkyl group.

Intermediates of formulae (i) – (ix) and any other intermediates required to obtain compounds of formulae (1), (2) or (3), if not available commercially, may be prepared by methods known to those skilled in the art following procedures set forth in references such as Rodd's Chemistry of Carbon Compounds, Volumes 1-15 and Supplementals (Eisevier Science Publishers,

1989), Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-19 (John Wiley and Sons, 1999), Comprehensive Heterocyclic Chemistry, Ed. Katritzky et al, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), Comprehensive Organic Functional Group Transformations, Ed. Katritzky et al, Volumes 1-7, 1995 Pergamon), Comprehensive Organic Synthesis, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), Encyclopedia of Reagents for Organic Synthesis Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and March's Advanced Organic Chemistry (John Wiley and Sons, 1992).

For example, an isocyanate or thioisocyanate of general formula (iii) may be prepared by reacting an amine of general formula (ii) with an appropriate reagent such as triphosgene, trichloromethyl chloroformate or thiophosgene using conditions known to those skilled in the art.

The amines of general formula (ii) when not commercially available may be prepared using well known literature methods.

It will be appreciated that compounds of formulae (1), (2) or (3) or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1), (2) or (3) where appropriate functional groups exist in these compounds.

For example, ester groups may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the ester. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous

methanol. Similarly an acid [-CO_2H] may be prepared by hydrolysis of the corresponding nitrile [-CN], using for example a base such as sodium hydroxide in a refluxing alcoholic solvent, such as ethanol.

In another example, -OH groups may be generated from a corresponding ester or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol. Alternatively an alcohol may be prepared by reduction of the corresponding acid [-CO_2H], using for example lithium aluminium hydride in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as an halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to the skilled artisan. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g., dichloromethane to yield the corresponding chloride. A base e.g., triethylamine may also be used in the reaction.

Aldehyde [-CHO] groups may be obtained by oxidation of a corresponding alcohol using well known conditions. For example using an oxidising agent such as a periodinane e.g Dess Martin, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane. An alternative oxidation may be suitably activating dimethyl sulfoxide using for example, oxalyl chloride, followed by addition of an alcohol, and subsequent quenching of the reaction by the addition of an amine base, such as triethylamine. Suitable conditions for this reaction may be using an appropriate solvent, for example, a halogenated hydrocarbon, e.g. dichloromethane at –78°C followed by subsequent warming to room temperature.

α,β-Unsaturated aldehydes, for example, of formula OHCE, where E is alkenyl or cycloalkenyl, may be prepared by hydrolysis of a corresponding allylic nitro compound. This may be achieved, for example, by treatment of the allylic nitro

compound with a base, such as sodium methoxide or potassium *tert*-butoxide, followed by addition of a buffered aqueous titanium trichloride solution. The allylic nitro compound may be prepared by nucleophilic addition of nitromethane to the corresponding ketone, followed by elimination of water. Suitable conditions for this reaction may be refluxing in toluene under Dean Stark conditions, in the presence of an amine base, such as N,N-dimethylethylene diamine. It will be appreciated that these aldehydes may be used in reductive alkylations to give compounds of formulae (1), (2) or (3), where Alk^3 is $-CH_2-$ using the conditions described herein.

In a further example primary amine ($-NH_2$) or secondary amine (-NH-) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney® nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol, e.g. methanol or ethanol,

optionally in the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride, e.g. lithium aluminium hydride, in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

N-oxides of compounds of formulae (1), (2) or (3) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formulae (1), (2) or (3) may be prepared by reaction of a compound of formulae (1), (2) or (3) with an appropriate base or acid in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using conventional procedures. Salts of compounds of formulae (1), (2) or (3) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of formulae (1), (2) or (3) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formulae (1), (2) or (3) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formulae (1), (2) or (3) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. The compounds are named with the aid of Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany.

^{1}H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

The following LCMS conditions were used to acquire the retention times as reported herein:

LCMS conditions:

HP1100 (Diode Array) linked to a Finnigan LcQ Duo Mass Spectrometer.

Column:	Luna C18(2) 100x4.6mm, 5µn particle size Analytical column
Column Temp:	35°C
Mobile Phase:	A: 0.08% formic acid in H_2O
	B: 0.08% formic acid in MeCN
Flow rate:	3ml/min

Gradient:	Time (mins):	% Composition B:
	0.0	95.0
	4.40	5.0
	5.30	5.0
	5.32	95.0
	6.50	95.0

Run time: 6.50 mins
Typical Injection Vol: 10µl
Detector Wavelength: 210nm

Abbreviations used:

DCM – Dichloromethane
THF – Tetrahydrofuran
MeOH – Methanol
EtOAc - Ethyl acetate
TFA – Trifluoroacetic acid
BOC – *tert*-butoxycarbonyl
$CDCl_3$ – Deuterated chloroform
DMSO-d_6 – Deuterated dimethylsulfoxide
Methanol-d_4 – Deuterated methanol
DMF – N,N-dimethylformamide

Intermediate 1

4-(Boc amino)-1-cycloocten-1-yl piperidine

4-Boc aminopiperidine hydrochloride (2 g) was dissolved in DCM (20 ml) and triethylamine (2 g) and triethylorthoformate (5 ml) were added. 1-Cyclooctene carboxaldehyde (CAS No. 6038-12-6) (2 g) was added and the mixture stirred for 30 min, then sodium triacetoxyborohydride (4 g) was added and the mixture stirred overnight at room temperature. The solution was washed with sodium bicarbonate, dried and evaporated to a beige solid 2.6 g.

TLC R_f 0.25 (5% MeOH/DCM)

Intermediate 2

4-Amino-1-cycloocten-1-ylpiperidine

TFA (10 ml) was added to a solution of 4-(boc amino)-1-cycloocten-1-yl piperidine (2.6 g) in DCM (30 ml) at room temperature. The solution was stirred for 2 h, then evaporated *in vacuo* and the residue dissolved in water and washed with ether. The aqueous layer was basified with sodium hydroxide pellets and extracted with DCM. The solvent was washed with water and brine, dried and evaporated to give the title compound as a pale yellow oil.

TLC R_f 0.22 (10%, MeOH/DCM 1% NH_4OH).

Similarly prepared was:

Intermediate 3

1-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethyl)piperidin-4-ylamine

From 4-boc amino piperidine (2 g) and 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carbaldehyde (2 g) to give the title compound as orange oil 2.4 g.

TLC R_f 0.30 (10% MeOH/DCM 1% NH_4OH).

Example 1

***N*-2-Naphthyl-*N'*-(cyclooctene-1-yl)methylpiperidine urea**

2-Naphthyl isocyanate (1 g) was added to a solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (1.2 g) in DCM and the solution was stirred for 24 h at room temperature. The mixture was evaporated *in vacuo* and the solid product triturated with ether. The residue was dissolved in DCM (50 ml) and TFA (10 ml) was added. The solution was stirred for 3 h, then evaporated *in vacuo* and the residue crystallised from methanol/ether. The solid product was dissolved in DCM (50 ml) and trimethyl orthoformate (10 ml) and triethylamine (1.5 ml) was added, followed by cyclooctene-1-aldehyde (1.2 g). The mixture was stirred for 1h, then sodium triacetoxyborohydride (3 g) was added. The resulting suspension was stirred overnight, then the mixture was filtered through Celite, washed with water and sodium bicarbonate solution and evaporated. The residue was crystallised from EtOAc/hexanes to give the title compound as colourless solid 0.85 g.

TLC R_f 0.35 (10% MeOH/DCM)

MS 391 (M^+)

Example 2

1-[1-((E)-1-Cyclooct-1-enyl)methylpiperidin-4-yl]-3-(3,4-dichlorophenyl)-urea

3,4-Dichlorophenyl isocyanate (100 mg) was added to a solution of 4-amino-1-cycloocten-1-ylpiperidine (100 mg) in DCM. Triethylamine (100 mg) was added and the solution was stirred overnight, washed with water and brine, then evaporated to dryness and triturated with ether to give the title compound as colourless solid (0.15 g).

[retention time 2.39 minutes]

R_f 0.40 (10% MeOH/DCM)

MS 410 (M+1)

Example 3

1-[1-((E)-1-Cyclooct-1-enyl)methyl-piperidin-4-yl]-3-(4-trifluoromethyl phenyl)-urea

4-Trifluoromethylphenyl isocyanate (100 mg) was added to a solution of 4-amino-1-cycloocten-1-ylpiperidine (100 mg) in DCM. Triethylamine was added and the mixture stirred overnight, washed with water and brine, dried and evaporated and the residue triturated with ether to give the title compound as colourless solid 0.12 g).

[retention time 2.36 minutes]

R_f 0.29 (10% MeOH/DCM)

MS 410 (M+1)

Similarly prepared from 4-amino-1-cycloocten-1-ylpiperidine and the appropriate isocyanate were:

Example 4

1-(3-Cyanophenyl)-3-[1-((E)-1-cyclooct-1-enyl)methylpiperidin-4-yl]-urea

Retention time 2.06 minutes

R_f 0.30 (10% MeOH/DCM)

MS 367 M+1

Example 5

1-Benzo[1,3]dioxol-5-yl-3-[1-((E)-1-cyclooct-1-enyl)methylpiperidin-4-yl]-urea

Retention time 2.01 minutes

R_f 0.26 (10% MeOH/DCM)

MS 386 M+1

Example 6

1-[1-((E)-1-Cyclooct-1-enyl)methylpiperidin-4-yl]-3-(4-phenoxyphenyl)-urea

Retention time 2.43 minutes

R_f 0.37 (10% MeOH/DCM)

MS 434 (M+ 1)

Example 7

1-Benzhydryl-3-[1-((E)-1-cyclooct-1-enyl)methylpiperidin-4-yl]-urea

Retention time 2.37 minutes

R_f 0.42 (10% MeOH/DCM)

MS 432 (M+1)

Example 8

1-Biphenyl-4-yl-3-[1-((E)-1-cyclooct-1-enyl)methylpiperidin-4-yl]-urea

Retention time 2.45 minutes

R_f 0.37 (10% MeOH/DCM)

MS 418 (M+1)

Example 9

1-[1-((E)-1-Cyclooct-1-enyl)methylpiperidin-4-yl]-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)-urea

Retention time 2.53 minutes

R_f 0.40 (10% MeOH/DCM)

MS 472 (M+1)

Example 10

1-[1-((E)-1-Cyclooct-1-enyl)methylpiperidin-4-yl]-3-indan-5-yl-urea

Retention time 2.27 minutes

R_f 0.33 (10% MeOH/DCM)

MS 382 (M+1)

Example 11

1-(4-Cyanophenyl)-3-[1-((E)-1-cyclooct-1-enyl)methylpiperidin-4-yl]-urea

Retention time 2.06 minutes

R_f 0.25 (10% MeOH/DCM)

MS 367 (M+1)

Example 13

1-[-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethyl)piperidin-4-yl]-3-naphthalen-2-yl urea

Prepared from 1-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethyl)piperidin-4-ylamine (100 mg) and 2-naphthyl isocyanate (100 mg) as white solid 0.13 g

Retention time

R_f 0.37 (10% MeOH/DCM)

MS 404 (M+1)

Chemokine calcium assay

The following assay may be used for to determine the inhibition of binding of a chemokine to its receptor:

CHO cells stably transfected with the human CXCR3 were seeded in a 96 well, blackwalled, clear bottomed tissue culture plate and incubated overnight at 37°C in the presence of 5% CO_2. The culture medium was gently removed from the well and replaced with wash buffer (Hank's Balanced Salts Solution with 0.2% BSA and 20 mM HEPES pH 7.2) containing 3μM Fluo-4 and 0.03% pluronic acid. The plate was incubated at 37°C for 1-2 hours, gently washed and 100μl wash buffer added per well.

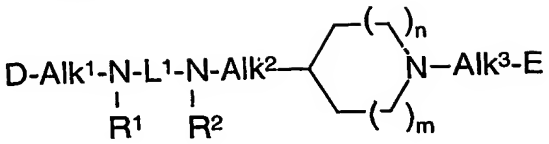
Test compounds were dissolved in DMSO and further diluted in wash buffer to give a DMSO concentration of 0.8% (reduced to 0.2% when added to the assay plate in the FLIPR™).

The assay was performed using a FLIPR™ (Molecular Devices). Compound was added to the assay plate after a 10 second baseline. Diluted human recombinant ITAC, IP-10 or MIG was added after a further 2 minutes. Compound activity was calculated as a percentage inhibition of a DMSO solvent control.

Compounds of the invention, for example, the compounds of the Examples, are able to inhibit the binding of chemokines to receptors in this assay, with an activity of >50% at 5μM. For example, the inhibition of the binding of ITAC, IP-10 or MIG to their receptor (CXCR3) with an activity of >50% at 5μm.

CLAIMS

1. A compound of formula (1):



(1)

wherein:

m and n, which may be the same or different, is each zero or the integer 1 or 2;

Alk^1 is a covalent bond or an optionally substituted aliphatic chain;

Alk^2 and Alk^3, which may be the same or different, is each a covalent bond or a straight or branched C_{1-6} alkyl chain;

R^1 and R^2, which may be the same or different, is each a hydrogen atom or a straight or branched C_{1-6} alkyl group;

L^1 is a linker group selected from –CO-, -CS-, $-SO_2-$ or $-C(=NR^3)-$, wherein R^3 is a –CN, $-COR^4$, $-OR^5$, $-CON(R^6)R^7$, SO_2R^4 or $SO_2N(R^6)R^7$ group, in which R^4 is an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, R^5 is a hydrogen atom or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group and R^6 and R^7, which may be the same or different, is each a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

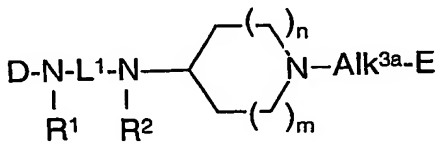
D is an optionally substituted aromatic or heteroaromatic group;

E is a substituted C_6 cycloalkyl or an optionally substituted C_{7-10} cycloalkyl, C_{6-10} cycloalkenyl, C_{6-10} polycycloaliphatic, C_{6-10} heterocycloaliphatic or C_{6-10} heteropolycycloaliphatic group;

and the salts, solvates, hydrates, tautomers or N-oxides thereof;

for use in the treatment of a CXCR3 mediated disorder.

2. A use according to Claim 1 of a compound of formula (2):



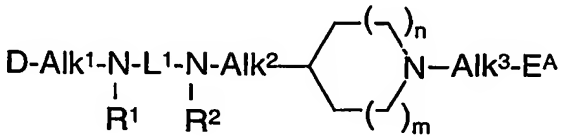
(2)

wherein m,n, R^1, R^2, L^1, D and E are as defined in Claim 1;

Alk^{3a} is a C_{1-3} alkyl chain;

and the salts, solvates, hydrates, tautomers or N-oxides thereof.

3. A compound of formula (3):



(3)

wherein:

m and n, which may be the same or different, is each zero or the integer 1 or 2;

Alk^1 is a covalent bond or an optionally substituted aliphatic chain;

Alk^2 and Alk^3, which may be the same or different, is each a covalent bond or a straight or branched C_{1-6} alkyl chain;

R^1 and R^2, which may be the same or different, is each a hydrogen atom or a straight or branched C_{1-6} alkyl group;

L^1 is a linker group selected from –CO-, -CS-, $-SO_2-$ or $-C(=NR^3)-$, wherein R^3 is a –CN, $-COR^4$, $-OR^5$, $-CON(R^6)R^7$, SO_2R^4 or $SO_2N(R^6)R^7$ group, in which R^4 is an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, R^5 is a hydrogen atom or an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group and R^6 and R^7, which may be the same or different, is each a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

D is an optionally substituted aromatic or heteroaromatic group;

E^A is an optionally substituted C_{7-10} cycloalkyl, C_{6-10} cycloalkenyl, C_{6-10} polycycloaliphatic, C_{6-10} heterocycloaliphatic or C_{6-10} heteropolycycloaliphatic group; or E^A is additionally a substituted C_6 cycloalkyl group when the sum of m+n is zero or 2, 3 or 4;

and the salts, solvates, hydrates, tautomers or N-oxides thereof;

4. A compound according to any preceding Claim wherein m and n, which may be the same or different, is each zero or the integer 1.

5. A compound according to Claim 4 wherein m and n are both the integer 1.
6. A compound according to any preceding Claim wherein Alk^3 or Alk^{3a} is a $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ chain.
7. A compound according to Claim 6 wherein Alk^3 or Alk^{3a} is a $-CH_2-$ chain.
8. A compound according to any preceding Claim wherein L^1 is –CO- or –CS.
9. A compound according to Claim 8 wherein L^1 is –CO-.
10. A compound according to any preceding Claim wherein R^1 and R^2, which may be the same or different, is each a hydrogen atom or a methyl group.
11. A compound according to any preceding Claim wherein D is optionally substituted phenyl, 1- or 2-naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, quinolinyl or isoquinolinyl.
12. A compound according to Claim 11 wherein D is an optionally substituted phenyl or 2-naphthyl group.
13. A compound according to any preceding Claim wherein E is an optionally substituted cycloheptyl, cyclooctyl, cyclononyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]heptenyl, bicyclo[3.1.1]heptanyl or bicyclo[3.1.1]heptenyl group.
14. A compound according to Claim 13 wherein E or E^A is a 1-cyclooctenyl or 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl group.
15. A pharmaceutical composition comprising a compound according to any of Claims 1 to 14 together with one or more pharmaceutically acceptable carriers, excipients or diluents.
16. A compound according to any of Claims 1 to 15 for use in the treatment of inflammatory, autoimmune and immunoregulatory disorders.